CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Zinc 2-Pyridinethiol-1-Oxide
Chemical Code # 2128 , **Tolerance #** 50651
SB 950 # 342
Copper 2-Pyridinethiol-1-Oxide
Chemical Code # 5975 , **Tolerance #** 53055
SB 950 # NA

2/3/09

I. DATA GAP STATUS

Chronic toxicity, rat:	Study not submitted*
Chronic toxicity, dog:	Study not submitted*
Oncogenicity, rat:	Study not submitted*
Oncogenicity, mouse:	Study not submitted*
Reproduction, rat:	Study not submitted*
Teratology, rat:	No data gap, no adverse effect indicated
Teratology, rabbit:	No data gap, no adverse effect indicated
Gene mutation:	No data gap, no adverse effect indicated
Chromosome effects:	No data gap, no adverse effect indicated
DNA damage:	No data gap, no adverse effect indicated
Neurotoxicity:	Data gap, possible adverse effect indicated

Toxicology one-liners are attached.

All record numbers through 237520 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T090203
Revised by T. Moore, 2/3/09

* Copper 2-Pyridinethiol-1-Oxide has been classified as an antimicrobial for purposes of toxicological requirements by US EPA. See discussion below. No other studies are required at this time to satisfy SB950 data requirements for Copper 2-Pyridinethiol-1-Oxide.

For the purposes of toxicity testing, Zinc 2-Pyridinethiol-1-Oxide and Copper 2-Pyridinethiol-1-Oxide have been classified by US EPA as antimicrobials, hence, requiring a more limited battery of studies (see US EPA Data Call-in Notice for Antimicrobial Pesticide Active Ingredients, January, 1987). The studies which are required in Tier I are 90-day feeding or dermal toxicity study, developmental toxicity study (1 species), and a genotoxicity battery. Listed below are summaries of those relevant studies on file with DPR as of 2/3/09.

The toxicity profiles of the two active ingredients are sufficiently similar to permit their grouping for the fulfillment of SB950 toxicity data requirements.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

Study not submitted.

CHRONIC TOXICITY, RAT

Study not submitted.

CHRONIC TOXICITY, DOG

Study not submitted.

ONCOGENICITY, RAT

Study not submitted.

ONCOGENICITY, MOUSE

Study not submitted.

REPRODUCTION, RAT

Study not submitted.

TERATOLOGY, RAT

** 013, 022; 125067, 155752; “Developmental Toxicity Study in Rats with Zinc Omadine”; (J.L. Schardein; International Research and Development Corporation, Mattawan, MI; Project No. 397-055; 5/27/93); Zinc Omadine FPS (Batch 33-22902781, 52.2% purity); 0, 0.75, 3.0, 15.0 mg/kg/day oral gavage; 30 mated female Crl:CD VAF/Plus rats/dose; observations-a single mortality in the high dose group occurred with decreased weight gain and increased salivation noted in both the mid and high dose groups, dilated pupils were also noted in approximately half the high dose animals; statistically significant increased developmental toxicity was present in the mid and high dose groups most noteworthy were vertebral malformation, fused sternebra and sternal malformation; no adverse effects; **Maternal NOEL** = 0.75 mg/kg (based on decreased maternal weight gain, food consumption, and increased salivation), **Developmental NOEL** = 0.75 mg/kg (based on total malformations/fetus); Study previously unacceptable possibly upgradeable with the submission of information detailing the composition of the test material and the analysis of the dosing solutions; requested information submitted; **Study acceptable.** (Miller, 10/13/94, upgraded, Moore, 8/29/97)

50651-015; 125069; "Range-Finding Developmental Toxicity Study in Rats with Zinc" (Author: J.L. Schardein; International Research and Development Corp., Mattawan, MI, Project No. 397-053, 5/11/93); Zinc Omadine FPS (Batch 33-22902781, 48% purity); 0, 0.75, 2.0, 5.0, 10.0, 15.0 mg/kg/day oral gavage; 5 mated female Crl;CD VAF/Plus rats/dose; observations-a decrease in maternal body weight gain was noted in the three highest dose groups, animals in the higher dose groups (3F,5.0 mg/kg; 1F,15.0 mg/kg) also showed impaired limb function; reduced relative fetal body weight was evident at dosage levels of 5.0, 10.0, and 15.0 mg/kg; **Maternal NOEL =** 2.0 mg/kg (based on decreased maternal weight gain); **Supplemental.** (Miller, 10/18/94)

TERATOLOGY, RABBIT

** 014, 022; 125068, 155753; "Developmental Toxicity Study in New Zealand White Rabbits with Zinc Omadine"; (J.L. Schardein; International Research and Development Corporation, Mattawan, MI; Project No. 397-056; 5/18/93); Zinc Omadine (52.2% Zinc 2-Pyridinethiol-1-Oxide); 0, 0.5, 1.5, 3.0 mg/kg/day oral gavage; 20 NZW SPF female rabbits/dose; observations-; one doe in the mid-dose group died; significant decreases in feed consumption was observed in the 1.5 and 3.0 mg/kg group (77.2 - 84.3% of control, $p<0.01$); decreased fetal survival was noted in the two highest dose groups, one abortion occurred in the high dose group, increased post-implantation loss (complete litter resorption) occurred in both the two highest dose groups; multiple cephalic and limb malformations occurred in three fetuses from 2 of 7 litters examined in the 3.0 mg/kg group. No additional physiological or developmental effects were observed at any other dose level; no adverse effect; **Maternal NOEL** = 0.5 mg/kg (based on decreased food consumption, trend of decreased weight loss), **Developmental NOEL** = 0.5 mg/kg (based on increased litter resorption, teratological effects); Study previously unacceptable, possibly upgradeable with the submission of information detailing the composition of the test material and the analysis of the dosing solutions; requested information submitted; **Study acceptable.** (Miller, 11/1/94, upgraded, Moore, 8/29/97)

50651-016; 125070; "Range-Finding Developmental Toxicity Study New Zealand White Rabbits with Zinc Omadine" (Author: J.L. Schardein; International Research and Development Corp., Mattawan, MI, Project No. 397-054, 5/11/93); Zinc Omadine FPS Batch 33-22902781, 52.2% purity; 0, 0.5, 2.0, 4.0, 8.0, 12.0 mg/kg/day oral gavage on days 6 through 18 of gestation; 5 mated female New Zealand White SPF rabbits/dose; observations-excessive maternal mortality was present at dosage levels of 8.0 (4/5) and 12.0 (5/5) mg/kg, maternal body weight loss was also noted in the 4.0 and 8.0 mg/kg dose levels; fetal post-implantation loss was increased at doses of 2.0 mg/kg and above based on the results of this range-finding study, dose levels of 0.5, 1.5, and 3.0 mg/kg/day were selected for the definitive developmental toxicity study; **no adverse effects indicated**; **Supplemental.** (Miller, 10/20/94)

GENE MUTATION

** 53055-0005; 237494; "A Bacterial Reverse Mutation Test of Copper Pyrithione"; (K. Ohta; Shin Nippon Biomedical Laboratories, Ltd., Kagoshima 891-13, Japan; Study No. SBL 40-37; 01/22/93);
S. typhimurium strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2*uvr*A were treated with Copper Pyrithione technical (batch no. 9302095981; purity: 99.7%) at concentrations ranging from 0.078 to 5 ug/plate with plate incorporation for 48 hours at 37^{O} C under conditions of non-activation. Under conditions of activation, the bacterial strains were exposed to concentration of the test material ranging from 0.469 to 15 ug/plate. Two trials were performed with duplicate samples for each treatment level. A phenobarbital and 5,6-benzoflavone-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 10/9/08)

** 53055-0008; 237520; "*In Vitro* Mammalian Cell Gene Mutation Test (CHO/HGPRT Assay)"; (R.H.C. San, J.J. Clarke; BioReliance, Rockville, MD; Study No. AA59XG.782.BTL; 10/10/02); Chinese hamster ovary cells were treated with Copper Pyrithione technical (no batch no. given; purity: 96.4%) at concentrations ranging from 0.015 to 0.1 µg/ml for 5 hours at 37^{o} C without activation and from 0.25 to 0.8 ug/ml with activation. A single trial was performed with duplicate cultures for each treatment level. Following a 7 to 9 day expression period, each culture was exposed to 6-thioguanine for selection of the mutant phenotype. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. There was no apparent treatment-related increase in the incidence of forward mutation. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 10/20/08)

** 006, 023; 121763, 155754; "*Salmonella*/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with a Confirmatory Assay"; (R.H.C. San and J.B. Shelton;

Microbiological Associates, Inc., Rockville, MD; Study No. T9153.501014; 10/19/90); 2-Mercaptopyridine-N-Oxide Zinc (test article #T9153, 48% purity) tested with *Salmonella typhimurium* strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100 with and without microsomal enzymes derived from Aroclor 1254 induced rat liver; triplicate plates two trials for nonactivated and activated systems with confirmatory assay; dose range 0-333 µg/plate; 48 hour incubation; postive controls functional; no increase in reversion rate reported; Study previously unacceptable, possibly upgradeable with the submission of the composition of the test material; requested information submitted; **Study acceptable.** (Miller, 11/4/94, upgraded, Moore, 8/29/97)

** 006, 023; 121765, 155754; "CHO/HGPRT Mutation Assay with Confirmation" (D. Jacobson-Kram & C.I. Sigler, Microbiological Associates Inc., Rockville, MD, study No. T9153.332001, 9/6/90); 2-Mercaptopyridine-N-Oxide Zinc (Lot # 9RC-290-109ZP, 48% purity); tested in Chinese hamster ovary cells with and without activation by Aroclor 1254 induced rat liver S-9 fraction; 18-24 hr (without activation) and 5 hr (with activation) incubations; triplicate plates two trials for activated and nonactivated systems; dose range 0-30 ug/ml; positive controls functional; no increase in mutant colonies were reported; Study previously unacceptable, but possibly upgradeable with submission of the exact composition of the test material; requested information submitted; **Study acceptable.** (Miller, 11/16/94, upgraded, Moore, 9/2/97)

CHROMOSOME EFFECTS

** 53055-0005; 237496; “A Chromosomal Aberration Test of Copper Pyrithione in Cultured Chinese Hamster Cells”; (K. Ohta; Shin Nippon Biomedical Laboratories, Ltd., Kagoshima 891-13, Japan; Study No. SBL 40-38; 10/22/93); Chinese Hamster Lung cells (CHL/IU) were incubated with copper pyrithione technical (batch no. 9302095981; purity: 99.7%) at concentrations ranging from 0.0025 to 0.01 ug/ml (nonactivated, 6 hours of treatment followed by 18 hours of incubation, 24 hours of treatment), 0.001 to 0.0075 ug/ml (non-activated, 48 hours of treatment), and 0.25 to 1.0 ug/ml (activated, 6 hours of treatment, 18 hours of incubation) at 37^{o} C. In all of the assays, the cells were incubated the last 2 hours with Colcemid prior to fixation. All of the incubations were performed with duplicate cultures. A phenobarbital and 5,6-benzoflavone-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the percentage of cells with chromosomal aberrations in any of the assays. **No adverse effect indicated.** The positive controls were functional for all of the assays except for the 6 hours of treatment under conditions of non-activation. **Study acceptable.** (Moore, 10/8/08)

53055-0005; 237497; “An *In Vitro* Chromosomal Aberration Test of Copper Pyrithione on the Peripheral Lymphocytes of Cynomologous Monkeys”; (K. Ohta; Shin Nippon Biomedical Laboratories, Ltd., Kagoshima 891-13, Japan; Study No. SBL 40-41; 10/22/93); Primary cultures of cynomologous monkey lymphocytes in whole blood, stimulated with phytohemaglutinin-M, were incubated with copper pyrithione technical (batch no. 9302095981; purity: 99.7%) at concentrations ranging from 0.313 to 2.5 ug/ml (nonactivated, 3 hours of treatment followed by 21 hours of incubation), from 0.0.063 to 1.0 ug/ml (non-activated, 24 hours of treatment), from 0.031 to 0.5 ug/ml (non-activated, 48 hours of treatment), and from 0.313 to 2.5 ug/ml (activated, 3 hours of treatment, 21 hours of incubation). In all of the assays, the cells were incubated the last 3 hours with Colcemid (0.1 ug/ml) prior to fixation. All of the incubations were performed with duplicate cultures. Separate lymphocyte cultures were derived from two monkeys. A phenobarbital and 5,6-benzoflavone-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the percentage of cells with chromosomal aberrations in any of the assays. **No adverse effect indicated.** The positive controls were functional for all of the assays except for the 3 hours of treatment under conditions of non-activation. **Study acceptable.** (Moore, 10/9/08)

** 006, 023; 121764, 155754; "Micronucleus Cytogenetic Assay In Mice" (D.L. Putman and M.J. Morris, Microbiological Associates Inc., Bethesda, MD, Study No. T9153.122, 10/22/90); 2-Mercaptopyridine-N-Oxide Zinc (Lot # 9RC-290-109ZP, 48% purity); IRC mice; 5 mice/sex/dose; 0, 11, 22, 44 mg/kg administered intraperitoneally; triethylenemelamine 0.25 mg/kg; positive control functional; bone marrow cells collected at 24, 48, and 72 hrs after

treatment; 1000 polychromatic erythrocytes/mice/dose examined for micronuclei; no statistically significant increase in micronucleus frequency at any dose level of 2-Mercaptopyridine-N-Oxide Zinc, one male mouse of the 44 mg/kg group died and was replaced with an animal from the 44 mg/kg replacement group; Study previously unacceptable, possibly upgradeable with submission of the test material's composition; requested information submitted; **Study acceptable.** (Miller, 11/9/94, upgraded, Moore, 8/29/97).

DNA DAMAGE

See 50651-0006, rec. no. 121764 above.

NEUROTOXICITY

53055-0003; 237488; "Oral (Gavage) Subchronic Neurotoxicity Study of Copper Omadine (CuPT) in Rats"; (J.F. Barnett; Charles Rivers Laboratories, Preclinical Services, Horsham, PA; Study No. AEN00008; 12/29/06); Sixteen Crl:CD(SD) rats/sex/group were dosed orally by gavage with 0 (aqueous 0.5% (w/v) carboxymethyl cellulose) or 2.25 mg/kg/day of Copper Omadine (lot no. 0103239911; purity: 96.8%) for 91 days. Ten animals/sex/group were dosed in the same manner with 0.5 or 1.25 mg/kg/day of the test material. Ten animals/sex in the control and 2.25 mg/kg groups were maintained for a recovery satellite cohort for an additional 6 weeks without treatment. One male in the 1.25 mg/kg group was found dead on study day 48. One female in the 2.25 mg/kg group was euthanized on day 89. No treatment-related effects were noted on the mean body weights or food consumption. No treatment-related lesions were evident in the ophthalmology examination. The FOB and motor activity measurements did not reveal any treatment-related effects over the course of the study. Electrophysiological measurements of nerve conduction in the sural nerve demonstrated a decreased amplitude in both sexes of the 2.25 mg/kg group at the termination of the dosing period and for the females in this group at the conclusion of the recovery period ($p<0.01$ or 0.05). The calf muscle mass of both sexes in the 2.25 mg/kg was less than that of the controls by week 5 in the males and by week 4 for the females ($p<0.01$). The effect was evident in both sexes through to the conclusion of the dosing. Thereafter the males recovered, but the effect was noted in 8 of the 9 surviving females at the end of the recovery period ($p<0.01$). In the histopathological evaluation, lesions were noted in the skeletal muscle of both sexes in the 2.25 mg/kg group. Minimal to mild myositis was noted in the gastrocnemius muscle ((M) 0: 0/5 vs. 2.25: 2/5, (F) 0: 0/5 vs. 2.25: 1/4). Minimal to moderate muscle fiber atrophy was evident ((M) 0: 0/5 vs. 2.25: 1/5, (F) 0: 0/5 vs. 2.25: 3/4). In addition, mild muscle fiber degeneration and minimal muscle fiber necrosis was noted in two males and one female, respectively, of the 2.25 mg/kg group. **Possible adverse effect:** muscle fiber necrosis. **Rat Subchronic Neurotoxicity NOEL:** can not be assigned; **Study unacceptable**, possibly upgradeable with the histological examination of the muscle tissue recovered from the low and intermediate treatment groups. (Moore, 9/25/08)

METABOLISM STUDIES

Metabolism, Rat

53055-0008; 237512; "*In Vivo* Dissociation of Copper Pyrithione (CuPT) in Female Rats"; (J.L. Valentine; Bioorganic Chemistry, Chemistry and Life Sciences, RTI International, Research Triangle Park, NC; Project ID. 08363.000; 7/25/02, amended, 8/5/02); In the first study, three female Crl:CD rats/group were dosed orally by gavage with either 0, 3, 5, 8 or 11 mg/kg/day of unlabelled zinc pyrithione suspension (1.0 mg/ml) for 9 days or 0, 4, 6, 9 or 12 mg/kg/day of an unlabeled copper pyrithione suspension (0.8 mg/ml) for 9 days. In the 2nd study, 5 female rats/group were dosed orally by gavage with 5 mg/kg/day of the unlabeled zinc pyrithione preparation for 6 days followed by two daily doses of a zinc [^{14}C] pyrithione suspension (1.0 mg/ml, specific activity: 9.98 mCi/mmol, 32.2 uCi/g) or 4 mg/kg/day of the unlabeled copper pyrithione preparation for 6 days, followed by two daily doses of a copper [^{14}C] pyrithione suspension (0.8 mg/ml, specific activity: 9.98 mCi/mmol, 25.6 uCi/g). The vehicle used for these dosing preparations was aqueous 0.5% Darvan. In the 2nd study, feces and urine were collected at 6, 12 and 24 hours after the first radiolabeled dose and up to 4 hour after the second dose. Total radioactivity was measured in the blood and carcass of these animals as well. Plasma and urine samples were sampled by HPLC and GC-MS for metabolites. In the **1st study**, one animal

in the 9 mg/kg group died on day 9. All of the treated animals displayed signs of irregular gait and lethargy by day 8. In the more severe cases at the higher treatment levels, paralysis was evident. The mean body weights of all of the copper pyrithione-treated groups were less than their initial weights by the end of the treatment period. In the zinc pyrithione groups, only the 3 mg/kg group gained weight over the course of the treatment. Assessment of muscle mass revealed a more severe effect on the animals treated with copper pyrithione. Greatly reduced muscle mass was noted for all of the treated animals except for one animal in the 12 mg/kg group. For the animals treated with zinc pyrithione, none of the animals demonstrated a greatly reduced muscle mass. In contrast, the muscle tone of the zinc pyrithione-treated animals was more affected than that of the copper pyrithione animals. In the **2nd study**, the mean body weights of both groups were less than than their initial weights by the end of the treatment period. Clinical signs ranged from slight lethargy to being non-responsive, prostrate and salivating for both groups at 30 minutes post-dose. By 4 hours post-dose, these signs had largely been resolved. Among the copper pyrithione animals, muscle mass was slightly or highly reduced in 4 of the 5 animals. Only two animals in the zinc pyrithione group suffered slightly or highly reduced muscle mass. In contrast, all of the zinc pyrithione-treated animals suffered moderate loss of muscle tone while two animals in the copper pyrithione-treated animals had moderate or high loss of muscle tone. The urine was the primary route of excretion of the radiolabel for both test materials. Sixty to 64% of the initial administered radiolabel dose was recovered within 24 hours post-dose in the urine. Only 1 to 2% of that first dose was in the feces. When the animals were euthanized, 50 to 57% of the total administered dose was recovered from the tissues. The metabolic profiles were similar for the two test materials with the major metabolite being identified as 2-methylsulfonyl pyridine. **Study supplemental.** (Moore, 10/15/08)

53055-0008; 237515; "Zinc Pyridinethione: Urinary Metabolites of Zinc Pyridinethione in Rabbits, Rats, Monkeys, and Dogs after Oral Dosing"; (A.R. Jeffcoat, W.B. Gibson, P.a. Rodrigues, T.S. Turan, P.F. Hughes, M.E. Twine; Chemistry and Life Sciences Group, Research Triangle Park, NC and Proctor and Gamble Company, Miami Valley Laboratories, Cincinnati, OH; Toxicology and Applied Pharmacology 56, 141 - 154 (1980)); Male Sprague-Dawley rats, male beagle dogs, female New Zealand rabbits and female rhesus monkeys were dosed orally by gavage with zinc (^{14}C) pyrithinethione (labeled in the 2 and 6 positions of pyridine ring) (radiochemical purity: 98% (analyzed by TLC), specific activity: 26 mCi/mmol). For the excretion profile, 4 rats, dogs and rabbits and 2 monkeys were dosed with 1 mg/kg of the test material. Urine and feces were collected up to 72 hours (rats), 96 hours (dogs and rabbits) or 144 hours (monkeys). In addition, urinary metabolites were isolated and identified in the 0 to 24 hour collection interval from the same group of rats, from 2 additional dogs dosed with 6 mg/kg of the test material, from 3 additional rabbits and from 3 additional monkeys. Seventy five to 95% of the administered dose was recovered in the urine of the study animals (rabbit and rat demonstrating the lower recovery percentages and the monkey and dog having the higher recoveries). Three conjugated metabolites were the predominant radiolabeled compounds in the urine (2-pyridinethiol-1-oxide-S-glucoside, 2-pyridinethiol-S-glucuronide, and 2-pyridinethiol-1-oxide-S-glucuronide). These metabolites constituted 54 to 85% of the total radioactivity recovered in the 0 to 24 hour post-dose interval. **Summary Report.** (Moore, 11/18/08)

Metabolism, Human

53055-0008; 237514; "Pyrithione: Plasma Metabolite in Man"; (J.H. Wedig, S.J. Barbee, C. Mitoma; Olin Corporation, New Haven, CT, SRI International, Menlo Park, CA; Fundamental and Applied Toxicology 4, 497 - 498 (1984)); Blood samples were obtained from 9 human volunteers at the conclusion of their shift, working as chemical processors in the manufacture of of pyrithiones. Blood was recovered from 3 others as controls. 2-Methylsulfonyl-pyridine (2-MSP) was detected in the blood of those involved in the manufacturing process at a mean level of 3.1 $\pm$ 2.0 ng/ml. No 2-MSP was recovered from the blood of the controls. The study results indicate the feasibility of using 2-MSP as a biological marker of exposure to pyrithione. **Summary Report**. (Moore, 11/17/08)

Mechanistic Study

53055-0008; 237517; "Ultrastructural Study of Zinc Pyridinethione-Induced Peripheral Neuropathy"; (Z. Sahenk, J.R. Mendell; Division of Neurology and Dept. of Pathology, Ohio State University College of Medicine, Columbus, OH; J. Neuropathol. Exp. Neurol. 38, 532 - 550 (1979));
Thirty three male Sprague-Dawley rats received 166 ppm of zinc pyridinethione in the diet for 8 days to 2 months. Animals were observed daily for signs of neurologic dysfunction. At specific times throughout the study, animals were euthanized by whole-body perfusion and selected peripheral nerves were dissected and examined by means of both electron and light microscopy. A neurologic deficit was noted in which the hopping and extensor postural thrust reactions in the hind limbs were weakened by day 4 to 7 of the study. The placing of the hind limb was noted to be slower. The syndrome progressed to rear limb paralysis between 9 and 12 days of treatment. The fore limbs demonstrated only mild weakness at this time. The flexor and spinal reflexes of the rear limbs were absent by day 14 to 17. Superficial and deep pain sensation were still present even in paralyzed animals. Morphological abnormalities occurred between 7 and 10 days at the intramuscular nerves and motor nerve terminals of the gastrocnemius, lumbrical and intrinsic foot muscles. Terminal axons displayed an accumulation of tubulo-vesicular (T-V) profiles. The number of synaptic vesicles was reduced. Animals which were removed from the test diet at thie time were able to gain a full recovery within 5 to 7 days. Continued exposure to the test material resulted in an enlargement of the nerve terminals, filled with osmophilic and multivesicular bodies. Ultimately, the terminal axon degenerated, leaving only the terminal Schwann cell. As the T-V profiles accumulated in the nerve terminals, significant reduction in the presence of other organelles (neurotubules, neurofilaments, mitochondria) was noted. These organelles were concentrated in the center of the axon. As axonal degeneration progressed, axonal sprouts were noted within the intramuscular nerve bundles. The pathological changes moved in a distil to proximal direction. The myelin sheath was thinner in the paranodal regions. The larger diameter axons were more affected than were the smaller ones. In the central nervous system (CNS), occasional axons in the lateral funiculus of the lumbar and sacral segments of the spinal cord and the cerebellar vermis were swollen and contained T-V profiles. Otherwise, the CNS was not affected. No treatment-related lesions were noted in the sensory nerves. The pathological mechanism for the peripheral neuropathy remains to be elucidated. **Possible adverse effect:** peripheral neuropathy. **Summary Report.** (Moore, 11/19/08)

SUBCHRONIC STUDIES

Rat 4-Week Oral Toxicity Study

53055-0004; 237489; "A Repeated Dose Toxicity Study of Copper Pyrithione Administered Orally to Rats for 28 Days Followed by a 14-Day Recovery Period"; (M. Omori; Shin Nippon Biomedical Laboratories, Ltd., Kagoshima 891-13, Japan; Report No. SBL 40-46; 7/18/95); Five Crj:CD (SD) rats/sex/group were dosed orally by gavage with 0, 0.6, 2.5 or 10.0 mg/kg/day of Copper pyrithione (batch no. 9302095981; purity: 99.7%) daily for 28 days. An additional 5 animals/sex in the control and 10.0 mg/kg groups were dosed and maintained for a 2-week recovery period. Two females in the 10.0 mg/kg group were euthanized *in extremis* on day 17 of the dosing period. Another female in the same group was found dead on day 2 of the recovery period. The mean body weights of both sexes in the 10.0 mg/kg group were less than those of the control during the last 2 to 3 weeks of treatment ($p<0.05$ or 0.01). The mean food consumption of both sexes in this group was also less than the control group during this period ($p<0.01$). Clinical signs included emaciation, decrease in spontaneous activity, ataxic gait and/or paralysis of the hind limbs, and piloerection. These signs were limited to both sexes in the 10.0 mg/kg group. In the urinalysis, the urine pH of the 10 mg/kg females was at a lower range than that of the control group ($p<0.05$). No apparent treatment-related effects were evident in the hematology or clinical chemistry. In the necropsy evaluation, the mean relative kidney weights of both sexes in the 10.0 mg/kg group were greater than the control group ($p<0.5$). The mean relative adrenal, spleen, lung, and liver weights of the 10.0 mg/kg females were greater than the control values ($p<0.05$ or 0.01). There was no treatment-related effect on the organ weights of the recovery animals. In the histopathological examination, the accumulation of eosinophilic granules in the proximal tubules of the kidneys was more severe in the 10 mg/kg males than in

the control group (slight to moderate, 0: 1/5 vs. 10.0: 5/5). The effect was not evident in the recovery animals. Atrophy of calf muscle fibers was evident for both sexes in the 10.0 mg/kg group ((M) anterior tibial muscle, very slight, 0: 0/5 vs.10.0: 2/5, (F) gastrocnemius, soleus, flexor digitorium longus and anterior tibial, very slight to moderate, 0: 0/5 vs. 10.0: 5/5, $p<0.01$). For the males, no effects were noted in the recovery animals. The two survivors in the female group still had very slight to slight atrophy in the affected muscles after the two-week recovery. **Possible adverse effect:** muscle fiber atrophy. **Rat 4-Week Oral Toxicity NOEL:** (M/F) 2.5 mg/kg/day (based upon the incidence of muscle fiber atrophy and clinical signs noted for both sexes in the 10.0 mg/kg group). **Study supplemental** (not a guideline study). (Moore, 10/1/08)

Monkey 4-Week Oral Toxicity Studies

53055-0004; 237490; "A Repeated Dose Toxicity Study of Copper Pyrithione Administered Orally to Cynomologus Monkeys for 28 Days Followed by a 14-Day Recovery Period"; (S. Oneda; Shin Nippon Biomedical Laboratories, Ltd., Kagoshima 891-13, Japan; Study No. SBL 40-43; 6/20/94); Four cynomologus monkeys/sex/group were dosed orally by gelatin capsule with 0, 11, 22 or 44 mg/kg/day of Copper pyrithione (batch no. 9302095981; purity: 99.7%) for 28 days. A recovery cohort of two animals/sex/group were treated with 0 or 44 mg/kg/day of the test material at the same time and then were maintained for an additional two weeks without treatment. No deaths resulted from the treatment. Clinical signs included incidences of soft stools, diarrhea and/or abnormal stool color for the 22 and 44 mg/kg groups and loss of appetite for the 44 mg/kg group. These signs resolved over the course of the 2-week recovery period. The mean body weight gains of both sexes in the 44 mg/kg group were less than the control values (NS). In the hematology evaluation, the red blood cell counts of both sexes in the 22 and 44 mg/kg groups were lower than the control values after 1 and 4 weeks of treatment (NS, $p<0.05$). The hematocrit and hemoglobin concentrations of both sexes in the 22 and 44 mg/kg groups were less than the control values during the treatment period as well (NS, $p<0.01$). These parameters were still lower for the 44 mg/kg group in comparison the control values after the 2-week recovery period. In the clinical chemistry evaluation, the serum total bilirubin concentrations of both sexes in the 44 mg/kg group were less than those of the control group after 4 weeks of treatment ($p<0.05$). The serum triglyceride concentrations of both sexes in the 44 mg/kg group were elevated in comparison with the control values after both 1 and 4 weeks of treatment ($p<0.05$ or 0.01). The serum creatine phosphokinase activity levels of both sexes in the 44 mg/kg group were greater than those of the control group after either one week or 4 weeks of treatment ($p<0.05$). In the urinalysis, both sexes in the 44 mg/kg group and the females in the 22 mg/kg group demonstrated elevated levels of bilirubin in the urine after either one or 4 weeks of treatment. The males in the 44 mg/kg group also had higher levels of ketones in the urine after one week of treatment. The absolute and relative liver weights of both sexes in the 44 mg/kg group were greater than the control values after 4 weeks of treatment ($p<0.01$). The liver weights of both sexes in the 44 mg/kg group were still greater than the control values after the 2-week recovery period. No treatment-related lesions were noted in the histopathological examination. **Possible adverse effect:** reduction in red blood cell count, hematocrit and hemoglobin concentration. **Monkey 4-Week Oral Toxicity NOEL:** (M/F) 11 mg/kg/day (based upon the treatment-related effects on the hematology parameters of both sexes in the 22 mg/kg group); **Study supplemental.** (Moore, 12/26/08)

53055-0008; 237516; "A Repeated Dose Toxicity Study of Zinc Omadine Powder to Cynomologus Monkeys for 28 Days and Followed by a 2 Week Recovery Period"; (M. Funato; Nippon Biomedical Laboratories, Ltd., Kagoshima 891-13, Japan; Study No. SBL 40-32; 12/7/92); Four cynomologus monkeys/sex/group were dosed orally by gelatin capsule with 0, 5.5, 11 or 22 mg/kg/day of Zinc Omadine Powder (batch no. 9204084481; purity: 96.3%) for 28 days. A recovery cohort of two animals/sex/group were treated with 0 or 22 mg/kg/day of the test material at the same time and then were maintained for an additional two weeks without treatment. One female in the 22 mg/kg group died on day 10 of the study. Clinical signs which were limited to the animals in the 22 mg/kg group included incidences of soft stools, vomiting, diarrhea, decrease in spontaneous activity, and loss of appetite. The mean body weight gains of both sexes in the 22 mg/kg group were less than the control values (NS). In the hematology evaluation, the mean red blood cell counts, hematocrit and hemoglobin concentrations of both sexes in the 22 mg/kg group

were lower than the control values after 4 weeks of treatment ($p<0.01$). In conjunction with these effects, the mean corpuscular volume was increased for both sexes in the 22 mg/kg group ($p<0.05$ or 0.01) and the mean corpuscular hemoglobin concentration was reduced for both sexes in the 22 mg/kg group ($p<0.01$ or NS). The percentage of reticulocytes was increased for the 22 mg/kg females ($p<0.05$). No treatment-related effects were noted in the ophthalmologic examination or the clinical chemistry evaluation. In the urinalysis, the incidence of elevated ketones in the urine of both sexes in the 22 mg/kg was marginally higher than that observed for the control group after both one and 4 weeks of treatment. The mean relative liver weight of the 22 mg/kg males was greater than the control value after 4 weeks of treatment ($p<0.05$). No treatment-related lesions were noted in the histopathological examination. **Possible adverse effect:** reduction in red blood cell count, hematocrit and hemoglobin concentration. **Monkey 4-Week Oral Toxicity NOEL:** (M/F) 11 mg/kg/day (based upon the clinical signs and treatment-related effects on the hematology parameters of both sexes in the 22 mg/kg group); **Study supplemental.** (Moore, 1/26/09)

Rat Subchronic Dietary Toxicity Study

53055-0008; 237518; "Administration of Zinc Omadine (WIN 9546) in the Diet of Albino Rats for Three Months"; (M.A. Rennie, C.E. Hunt Jr., M.R. Donkiian; Sterling Winthrop Research Institute, address not provided; Study ID. PD. 2-543; 6/6/73); Twenty CD albino rats/sex/group received 0, 5, 25, or 125 ppm of Zinc Omadine technical (WIN 9546) (lot no. 97-P-158; purity: not reported) for 3 months ((M) 0, 0.35, 1.75, 10.04 mg/k/day, (F) 0, 0.39, 2.13, 10.26 mg/kg/day). Nineteen males and 20 females in the 125 ppm group died during the study between days 11 and 63. One male in the 5 ppm group died as a consequence of a non-treatment-related injury. Impairment of movement in the hindlimbs of the 125 ppm animals was first noted during the 2nd week of treatment and progressed to complete paralysis for all of the animals. No treatment-related clinical signs were evident for the 5 and 25 ppm treatment groups. The mean body weights and food consumption of both sexes in the 125 ppm group were less than the control group values throughout the study. The mean body weights of both sexes in the 25 ppm group were 5 to 10% less than the control values at the termination of the study. There was no apparent treatment-related effect on systolic pressure. The hematological and clinical chemical evaluations and urinalysis did not reveal any treatment-related effect. The mean relative organ weights were not affected by the treatment for the 5 and 25 ppm groups. No histological lesions were noted for these two treatment groups. **Possible adverse effect:** paralysis of the hindlimbs; **Rat Subchronic Dietary Toxicity NOEL:** (M/F) 5 ppm ((M) 0.35 mg/kg/day, (F) 0.39 mg/kg/day) (based upon lower mean body weights for both sexes in the 25 ppm group); **Study supplemental**; study predated guidelines for subchronic dietary studies. (Moore, 11/17/08)

Rat Repeated Dosing Subchronic Dermal Toxicity Study

50651-012; 125066; 823; Rat; "90-Day Subchronic Dermal Toxicity Study on Zinc Omadine in Rats"; C.E. Ulrich; International Research and Development Corporation Mattawan, MI; Report No. 397-057; 4/29/93; Zinc Omadine FSP (52.2% Zinc 2-Pyridinethiol-1-Oxide); 15/sex/dose; doses 0, 20, 100, 1000 mg/kg (applied 6 hrs/day, 5 days/week for 13 weeks on intact skin sites); observations-no mortalities or signs of dermal irritations were observed, food consumption was depressed for females dosed at 1,000 mg/kg; reduced body weight was noted for females dosed at 1,000 mg/kg (81.8% of control, $P<0.01$); no other significant effects were noted in the other groups for any parameter; **NOEL** (M) $\geq$ 1000 mg/kg (no effects at high dose treatment), (F) = 100 mg/kg (reduced body weight); Acceptable. (Miller, 10/7/94)

Rat 2-Week Inhalation Toxicity Study

50651-017; 125071; 813; Rat; "Two Week Range-Finding Inhalation Toxicity Study on Zinc Omadine in Rats"; C.E. Ulrich; International Research and Development Corporation Mattawan, MI; Report No. 397-058; 5/11/93; Zinc Omadine FPS (53% Zinc 2-Pyridinethiol-1-Oxide); 10/sex/dose; whole-body exposure to 0, 1.0, 3.6, 11, 43 mg/m^3 (actual concentrations, MMAD=1.5u, GSD=1.72, 6 hours/day, 5 days/week for two weeks); observations- due to excessive mortality observed at 43 mg/m^3 exposure level with deaths occurring one day post exposure this dose group was terminated on day 2; no additional deaths occurred in the other dose groups; mean weekly body weights of the 11 mg/m^3 group were significantly reduced

compared to controls; food consumption was significantly depressed for all 11 mg/m^3 exposure animals and lowest level males during the first week, food consumption during week 2 was also depressed for the 1 mg/m^3 and 11 mg/m^3 females and 1 mg/m^3 males; no test article macro or microscopic lesions were noted; **Supplemental**; (Miller, 10/24/94)

Rat Subchronic Inhalation Toxicity Study

50651-011; 125065; 824; Rat; "Thirteen Week Subchronic Inhalation Toxicity Study on Zinc Omadine in Rats"; C.E. Ulrich; International Research and Development Corporation Mattawan, MI; Report No. 397-052; 5/17/93; Zinc Omadine FPS (52.2% Zinc 2-Pyridinethiol-1-Oxide); 15/sex/dose; doses 0, 0.51, 2.5, 10 mg/m^3 (actual concentrations; MMAD: 1.2-1.5 microns, GSD: 1.66-1.75); whole-body exposure 6 hours/day, 5 days/week for thirteen weeks; observations-nine animals died (1M,1F at 2.5 mg/m^3 and 3M,4F at 10 mg/m^3), clinical signs included rales, labored breathing and gasping a few days to a week before death, body weight and food consumption was depressed for the 10 mg/m^3 treated females; lung weights were elevated and pulmonary inflammation was noted for both males and females exposed to levels at or above 2.5 mg/m^3; pulmonary arterial medial hypertrophy was observed in the 10 mg/m^3 animals; no other test article related biochemical or pathological lesions were noted; **NOEL** (M/F) = 0.51 mg/m^3 (based on increased lung weight and inflammation); **Acceptable**; (Miller, 10/26/94)